REMARKS

Objections to the Specification

Examiner's remarks are quoted below in small block type.

1. The disclosure is objected to because of the following informalities: the specification (p. 2-3 and 10) makes reference to an ATCC Accession Number that is not provided. Applicant is advised to review the entire specification for similar errors. Correction is required.

The specification has been amended to delete reference to an ATCC Accession Number.

3. The use of the trademark Taqman has been noted in this application (p. 13-14 and 119). It should be capitalized wherever it appears and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

The specification has been amended to note the trademark Taqman.

4. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code (p.14 and 17. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Embedded hyperlinks have been deleted from the specification.

5. This application filed under former 37 CFR 1.62 lacks the necessary reference to the prior application. A statement reading "This is a continuation in part of Application No. 09/633300, filed 8 August 200." should be entered following the title of the invention or as the first sentence of the specification. Also, the current status of the parent nonprovisional application(s)should be included.

The statement cross-referencing prior applications has been amended to recite 09/633,300.

Claims

Claims 19 and 54-62 are pending. Claims 19, 58, and 61 are rejected on substantive grounds. Applicants are unclear if claims 54-57, 59, 60, and 62 are rejected or objected to and, if so, on what grounds. Claims 63 to 68 are new. Support for claim 63 can be found, e.g., on page 57 and in original claim 20. Support for claim 64 can be found, e.g., on page 57, lines 10 to 15. Examiner's remarks are quoted below in small block type.

> **7. Claim 58 recites the limitation "14094" in line 1. There is insufficient antecedent basis for this limitation in the claim.**

Claim 58 has been amended to remove the term "14094."

> **8. Claim 58 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. It is not clear what steps are needed for a 14094-mediated proteolysis assay and how determining whether a test compound binds to SEQ ID NO: 12 is indicative of said assay.**

Claim 58 has been amended. Applicant submits that it is well established that a product of an enzymatic reaction is generated by binding of the substrate to the enzyme active site. Accordingly a binding interaction can be detected by evaluating cleavage of a test compound.

> **10. Claims 19 and 61 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.**
>
> **11. Factors to be considered in determining whether undue experimentation is required, are summarized in *Ex parte* Forman, *230* USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.**
>
> **12. Claim 61 recites using a test compound, which is a member of a biological library in the method of claim 19. The specification states that the test compounds may be obtained using numerous approaches in combinatorial library methods known in the art including biological libraries. This includes a whole universe of libraries and one cannot extrapolate the teachings of the specification to the breadth of the claims because the claims are broadly drawn to any biological library with or without the biological properties representative of what is claimed, and applicant has not enabled all of these types of modified libraries because it has not been shown that they are capable of functioning as that which is being disclosed. Reasonable correlation must exist between the breadth of the claims**

and the enablement set forth, and it cannot be predicted from the disclosure as to which biological libraries should be library should be used to select the test compound that is to be used in the method of claim 19. Therefore, in view of the lack of predictability of the prior art, lack of working examples, the breadth of the claims, and insufficient guidance as indicated above, one of skill in the art would not be able to practice the claimed invention because undue experimentation would be required.

The Examiner has rejected claim 19 and 61 for lack of enablement. Examiner's remarks are directed to claim 61, which is directed to a method that can be used to evaluate whether a test compound from a biological library can interact with a target polypeptide that includes the sequence of SEQ ID NO:12.

The Examiner alleges that claim 61 does not enable the claimed scope of biological libraries because one skilled in the art would not know which biological library to use. For example, the Examiner states: "it cannot be predicted from the disclosure as to which biological libraries should be library should be used" (page 4 of the Office Action). The claimed method is a method of evaluating a test compound from any biological library. Because the method informs both in the instance where binding is detect and in the instance where it is not detected, it is no argument that a particular library must be predicted a priori to include test compounds that give a particular result. One skilled in the art can use any biological library and evaluate one or more test compounds from it. The method indicates whether the evaluated compound interact with the target polypeptide. Further, the method could also be used to determine the likelihood that a particular library includes test compounds that do or do not interact with the target polypeptide.

The Examiner further alleges that "applicant has not enabled all of these types of modified[1] libraries because it has not been shown that they are capable of functioning as that which is being disclosed." (page 4 of the Office Action, emphasis added). The only function of the test compound required by claim 61 is that it be available for evaluation. In view of the high level of skill in the art of biological libraries at the time of filing of 60/200,621 (the priority application), the specification is sufficient to enable one skilled in the art to obtain a test compound from a biological library and evaluate it as claimed. Biological libraries such as

[1] Applicant is uncertain as to the meaning of the Examiner's term "modified." This term is not in claim 19 or 61. Applicant rejects any interpretation that the term "modified" limits the meaning of any pending claim.

phage display libraries (see, e.g., U.S. 5,223,409 (Item BA in the enclosed Supplemental Information Disclosure Statement), and page 58, lines 26-28 of the specification), peptide libraries (see, e.g., Houghten, Biotechniques 1992 Sep;13(3):412-21 (Item BP) and page 58, line 22), and antibody libraries (see, e.g., WO 92/20791 (Item BJ) and page 44, lines 8-21) were used with much success. Many such biological libraries were also commercially available and/or in commercial use. Applicants respectfully request that the § 112 enablement rejection of claim 61 be withdrawn.

With respect to claim 19, the claimed method does not require (nor exclude) the use of a biological library. Moreover, as seen above, claim 19 is also enabled when used to evaluate a test compound from a biological library. Applicants respectfully request that the § 112 enablement rejection of claim 19 be withdrawn.

13. Claims 19 and 61 are rejected under 35 U.S.C. 112, first paragraph. The instant specification does not contain a written description of the invention in such full, clear, concise, and exact terms or in sufficient detail that one skilled in the art can reasonably conclude that applicant had possession of the claimed invention at the time of filing.

***Vas-Cath Inc. v. Mahurkar* (CA FC)19 USPQ2d 1111 (6/7/1991)clearly states that "written description" of invention required by first paragraph of 35 U.S.C. 112 is separate and distinct from that paragraph's requirement of enabling disclosure, since description must do more than merely provide explanation of how to "make and use" invention; applicant must also convey, with reasonable clarity to those skilled in art, that applicant, as of filing date sought, was in possession of invention, with invention being, for purposes of "written description" inquiry, whatever is presently claimed. An applicant shows possession by describing the claimed invention with all it limitations using such descriptive means as words, structures, diagrams, and formulas. Also, description of an actual reduction to practice, or by showing the invention was "ready for patenting," or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention at the time of filing.**

The specification states that test compounds may be obtained using numerous approaches in combinatorial library methods known in the art including biological libraries, but does not guide or exemplify the isolation of and assaying of any biological library. There are no examples disclosed that conveys to one of skill in the art that the applicant was in possession of the claimed libraries. There is no actual reduction to practice, sufficient descriptive information, such as definitive structural features, complete detailed description of the function of claimed invention indicating that the library was indeed isolated, produced, and assayed for the uses disclosed. Thus, one skilled in the art would not recognize from the disclosure that the applicant was in possession of the claimed biological library or test compounds thereof.

Examiner's basis for the written description rejection is lack of possession of a "biological library or test compounds thereof." Claim 19, however, does not require a biological library or a test compound specifically from a biological library. Accordingly, Applicants respectfully request that the § 112 written description rejection of claim 19 be withdrawn.

Claim 61 does require a test compound from a biological library. The Written Description Guidelines provide an appropriate standard for evaluating whether the claimed invention is sufficiently described.

> The description need only describe in detail that which is new or not conventional.... What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail.

(Federal Register, Vol. 66, no. 4, page 1106, column 1, emphasis added)

With respect to claim 61, one element that is new is the polypeptide that comprises the sequence of SEQ ID NO:12. Biological libraries in and of themselves, however, are conventional and well known to one of ordinary skill in the art. Examples of libraries mentioned in the specification include phage display libraries (page 58, lines 26-28), peptide libraries (see, e.g., page 58, line 22), and antibody libraries (page 44, lines 8-21). These biological libraries were well described in the literature and need not be structurally described in the specification. See, e.g., U.S. 5,223,409, Houghten, Biotechniques 1992 Sep;13(3):412-21, WO 92/2079, and other references cited in the specification. Applicants respectfully request that the § 112 written description rejection of claim 61 be withdrawn.

Attached is a marked-up version of the changes being made by the current amendment.

Applicant asks that all claims be allowed. Please apply any charges or credits to Deposit Account No. 06-1050, referencing attorney docket number 10448-046002.

Respectfully submitted,

Date: 21 Oct 02

Louis Myers
Reg. No. 35,965

Fish & Richardson P.C.
225 Franklin Street
Boston, Massachusetts 02110-2804
Telephone: (617) 542-5070
Facsimile: (617) 542-8906

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Version with markings to show changes made

In the specification:

Please replace the paragraph beginning at page 1, line 5 with the following rewritten paragraph:

-- This application is a continuation-in-part of Application No. 09/633300, filed 8 August 2000, which claims the benefit of United States Provisional Patent Application No. 60/200,621, filed April 28, 2000, and United States Patent Application No. 09/633,300, filed August 8, 2000, the contents of which are hereby incorporated by reference. --

Please replace the paragraph beginning at page 2, line 11 with the following rewritten paragraph:

-- Accordingly, in one aspect, the invention features a nucleic acid molecule that encodes a 14094 protein or polypeptide, e.g., a biologically active portion of the 14094 protein. In a preferred embodiment the isolated nucleic acid molecule encodes a polypeptide having the amino acid sequence of SEQ ID NO:2 or SEQ ID NO:12. In other embodiments, the invention provides isolated 14094 nucleic acid molecules having the nucleotide sequence shown in SEQ ID NO:1, SEQ ID NO:11, SEQ ID NO:3, or SEQ ID NO:13 [or the sequence of the DNA insert of the plasmid deposited with ATCC Accession Number ____]. In still other embodiments, the invention provides nucleic acid molecules that are substantially identical (e.g., naturally occurring allelic variants) to the nucleotide sequence shown in SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:11, or SEQ ID NO:13 [or the sequence of the DNA insert of the plasmid deposited with ATCC Accession Number ____]. In other embodiments, the invention provides a nucleic acid molecule which hybridizes under a stringency condition described herein to a nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:11, or SEQ ID NO:13 [or the sequence of the DNA insert of the plasmid deposited with ATCC Accession Number ____], wherein the nucleic acid encodes a full length 14094 protein or an active fragment thereof. --

Please replace the paragraph beginning at page 3, line 11 with the following rewritten paragraph:

-- In other embodiments, the invention provides 14094 polypeptides, e.g., a 14094 polypeptide having the amino acid sequence shown in SEQ ID NO:2, or SEQ ID NO:12 [, or the amino acid sequence encoded by the cDNA insert of the plasmid deposited with ATCC Accession Number ___]; an amino acid sequence that is substantially identical to the amino acid sequence shown in SEQ ID NO:2, or SEQ ID NO:12 [or the amino acid sequence encoded by the cDNA insert of the plasmid deposited with ATCC Accession Number ___]; or an amino acid sequence encoded by a nucleic acid molecule having a nucleotide sequence which hybridizes under a stringency condition described herein to a nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:11, or SEQ ID NO:13 [or the sequence of the DNA insert of the plasmid deposited with ATCC Accession Number ____, wherein the nucleic acid encodes a full length 14094 protein] or an active fragment thereof.--

Please replace the paragraph beginning at page 8, line 18 with the following rewritten paragraph:

-- *Figure 4* is a bar graph depicting the expression of 14094 RNA in a panel of normal and tumor human tissues, including breast, colon, liver, and lung, detected using [TaqMan] TAQMAN® analysis. 14094 RNA expression in normal (solid bars) and malignant ("diseased"; hatched bars) tissues from the breast, colon, liver and lung is shown. Elevated expression of 14094 RNA was detected in malignant tissues relative to normal tissues. --

Please replace the paragraph beginning at page 8, line 23 with the following rewritten paragraph:

-- *Figure 5* is a bar graph depicting the expression of 14094 RNA in a panel of normal and tumor human ovarian samples, detected using [TaqMan] TAQMAN® analysis. Elevated expression of 14094 RNA was detected in malignant ovarian tissues relative to normal tissues. --

Please replace the paragraph beginning at page 8, line 27 with the following rewritten paragraph:

-- *Figure 6* is a bar graph depicting the expression of 14094 RNA in a panel of cell lines, detected using [TaqMan] TAQMAN® analysis. Elevated expression of 14094 RNA was detected in DLD-1 and SW 620 cells lines. Both DLD-1 and SW620 are cell lines derived from colorectal carcinomas. SW620 is a lymph node metastasis of a colorectal carcinoma. --

Please replace the paragraph beginning at page 10, line 22 with the following rewritten paragraph:

-- For general information regarding PFAM identifiers, PS prefix and PF prefix domain identification numbers, refer to Sonnhammer et al. (1997) Protein 28:405-420[and http://www.psc.edu/general/ software/packages/pfam/pfam.html]. --

Please replace the paragraph beginning at page 10, line 25 with the following rewritten paragraph:

-- A plasmid containing the nucleotide sequence encoding human 14094 (clone "Fbh14094FL") was deposited with American Type Culture Collection (ATCC), 10801 University Boulevard, Manassas, VA 20110-2209, on _____ and assigned Accession Number _____. This deposit will be maintained under the terms of the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure. This deposit was made merely as a convenience for those of skill in the art and is not an admission that a deposit is required under 35 U.S.C. §112.

Table 1: Summary of Sequence Information for 14094

Gene	cDNA	ORF	Polypeptide	[Figure]	[ATCC Accession #]
14094	SEQ ID NO:1,	SEQ ID NO:3	SEQ ID NO:2		
14094	SEQ ID NO:11	SEQ ID NO:13	SEQ ID NO: 12		

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Please replace the paragraph beginning at page 14, line 16 with the following rewritten paragraph:

-- As used herein, the term "trypsin domain" (or a "trypsin-chymotrypsin" domain) refers to a protein domain having an amino acid sequence of from about 50 to about 350 amino acid residues and having a bit score for the alignment of the sequence to the trypsin domain (HMM) of at least 80. Preferably, a trypsin domain includes at least about 100 to about 300 amino acids, more preferably about 150 to about 250 amino acid residues, about 200 to about 230, or about 226 amino acids and has a bit score for the alignment of the sequence to the trypsin domain (HMM) of at least 100, preferably at least 200, more preferably at least 220, and most preferably 250 or greater. The trypsin domain (HMM) has been assigned the PFAM Accession (PF00089)[(http://genome.wustl.edu/Pfam/.html)]. An alignment of the trypsin domain (from about amino acids 217 to about 443 of SEQ ID NO:2) of human 14094 with a consensus amino acid sequence derived from a hidden Markov model (PFAM) is depicted in Fig. 3A. An alignment of the trypsin domain (from about amino acids 217 to about 443 of SEQ ID NO:2) of human 14094 with a consensus amino acid sequence derived from another hidden Markov model (SMART) is depicted in Fig. 3B. --

Please replace the paragraph beginning at page 15, line 9 with the following rewritten paragraph:

-- To identify the presence of a "trypsin" domain in a 14094 protein sequence, and make the determination that a polypeptide or protein of interest has a particular profile, the amino acid sequence of the protein can be searched against a database of HMMs (e.g., the Pfam database, release 2.1) using the default parameters[(http://www.sanger.ac.uk/Software/Pfam/HMM_search)]. For example, the hmmsf program, which is available as part of the HMMER package of search programs, is a family specific default program for MILPAT0063 and a score of 15 is the default threshold score for determining a hit. Alternatively, the threshold score for determining a hit can be lowered (e.g., to 8 bits). A description of the Pfam database can be found in Sonhammer et al. (1997) Proteins 28(3):405-420 and a detailed description of HMMs can be found, for example, in Gribskov et

al.(1990) Meth. Enzymol. 183:146-159; Gribskov et al.(1987) Proc. Natl. Acad. Sci. USA 84:4355-4358; Krogh et al.(1994) J. Mol. Biol. 235:1501-1531; and Stultz et al.(1993) Protein Sci. 2:305-314, the contents of which are incorporated herein by reference. A search was performed against the PFAM HMM database resulting in the identification of a "trypsin domain" in the amino acid sequence of human 14094 at about residues 217 to about 443 of SEQ ID NO:2 with a bit score of 293 (see Figs. 1 and 3). --

Please replace the paragraph beginning at page 17, line 15 with the following rewritten paragraph:

-- As used herein, the term "scavenger receptor cysteine-rich domain" includes an amino acid sequence of about 80 to 120 amino acid residues in length and having a bit score for the alignment of the sequence to the scavenger receptor cysteine-rich domain (HMM) of at least 3. Preferably, a scavenger receptor cysteine-rich domain includes at least about 80 to 120 amino acids, more preferably about 87 to 110 amino acid residues, or about 90 to 100 amino acids and has a bit score for the alignment of the sequence to the scavenger receptor cysteine-rich domain (HMM) of at least 3 or greater. The scavenger receptor cysteine-rich domain (HMM) has been assigned the PFAM Accession Number PF00530[(http;//genome.wustl.edu/Pfam/.html)]. An alignment of the scavenger receptor cysteine-rich domain (amino acids 110 to 205 of SEQ ID NO:2) of human 14094 with a consensus amino acid sequence (SEQ ID NO:7) derived from a hidden Markov model is depicted in Figure 4B. --

Please replace the paragraph beginning at page 26, line 24 with the following rewritten paragraph:

-- The comparison of sequences and determination of percent identity between two sequences can be accomplished using a mathematical algorithm. In a preferred embodiment, the percent identity between two amino acid sequences is determined using the Needleman and Wunsch ((1970) J. Mol. Biol. 48:444-453) algorithm which has been incorporated into the GAP program in the GCG software package[(available at http://www.gcg.com)], using either a Blossum 62 matrix or a PAM250 matrix, and a gap weight of 16, 14, 12, 10, 8, 6, or 4 and a length weight of 1, 2, 3, 4, 5, or 6. In yet another preferred embodiment, the percent identity

between two nucleotide sequences is determined using the GAP program in the GCG software package[(available at http://www.gcg.com)], using a NWSgapdna.CMP matrix and a gap weight of 40, 50, 60, 70, or 80 and a length weight of 1, 2, 3, 4, 5, or 6. A particularly preferred set of parameters (and the one that should be used unless otherwise specified) are a Blossum 62 scoring matrix with a gap penalty of 12, a gap extend penalty of 4, and a frameshift gap penalty of 5. --

Please replace the paragraph beginning at page 27, line 8 with the following rewritten paragraph:

-- The nucleic acid and protein sequences described herein can be used as a "query sequence" to perform a search against public databases to, for example, identify other family members or related sequences. Such searches can be performed using the NBLAST and XBLAST programs (version 2.0) of Altschul, et al. (1990) J. Mol. Biol. 215:403-10. BLAST nucleotide searches can be performed with the NBLAST program, score = 100, wordlength = 12 to obtain nucleotide sequences homologous to 14094 nucleic acid molecules of the invention. BLAST protein searches can be performed with the XBLAST program, score = 50, wordlength = 3 to obtain amino acid sequences homologous to 14094 protein molecules of the invention. To obtain gapped alignments for comparison purposes, Gapped BLAST can be utilized as described in Altschul et al., (1997) Nucleic Acids Res. 25:3389-3402. When utilizing BLAST and Gapped BLAST programs, the default parameters of the respective programs (e.g., XBLAST and NBLAST) can be used. [See http://www.ncbi.nlm.nih.gov.] --

Please replace the paragraph beginning at page 32, line 1 with the following rewritten paragraph:

-- In preferred embodiments, nucleic acids include a nucleotide sequence which is about 311, 400, 500, 600, 700, 800, 900, 1000, 1100, 1200, 1300, 1400, 1500, 1600, 1700, 1800, 1900, 2000, 2100, 2200, 2300, 2400, 2500, 2600, 2700, 2800 or 2900 nucleotides in length and hybridizes under stringent hybridization conditions to a nucleic acid molecule of SEQ ID NO:1, SEQ ID NO:11, [or] SEQ ID NO:3, or SEQ ID NO:13 [or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number _____]. --

Please replace the paragraph beginning at page 33, line 32 with the following rewritten paragraph:

-- Moreover, nucleic acid molecules encoding other 14094 family members and, thus, which have a nucleotide sequence which differs from the 14094 sequences of SEQ ID NO:1, 11, 13, or 3, [or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number _____] are intended to be within the scope of the invention. --

Please replace the paragraph beginning at page 115, line 17 with the following rewritten paragraph:

-- Example 2: Tissue Distribution of 14094 mRNA by [TaqMan] TAQMAN® Analysis

Endogenous human 14094 gene expression was determined using the Perkin-Elmer/ABI 7700 Sequence Detection System which employs [TaqMan] TAQMAN® technology. Briefly, [TaqMan] TAQMAN® technology relies on standard RT-PCR with the addition of a third gene-specific oligonucleotide (referred to as a probe) which has a fluorescent dye coupled to its 5' end (typically 6-FAM) and a quenching dye at the 3' end (typically TAMRA). When the fluorescently tagged oligonucleotide is intact, the fluorescent signal from the 5' dye is quenched. As PCR proceeds, the 5' to 3' nucleolytic activity of Taq polymerase digests the labeled primer, producing a free nucleotide labeled with 6-FAM, which is now detected as a fluorescent signal. The PCR cycle where fluorescence is first released and detected is directly proportional to the

starting amount of the gene of interest in the test sample, thus providing a quantitative measure of the initial template concentration. Samples can be internally controlled by the addition of a second set of primers/probe specific for a housekeeping gene such as GAPDH which has been labeled with a different fluorophore on the 5' end (typically VIC). --

Please replace the paragraph beginning at page 115, line 32 with the following rewritten paragraph:

-- To determine the level of 14094 in various human tissues a primer/probe set was designed. Total RNA was prepared from a series of human tissues using an RNeasy kit from Qiagen. First strand cDNA was prepared from 1 μg total RNA using an oligo-dT primer and Superscript II reverse transcriptase (Gibco/BRL). cDNA obtained from approximately 50 ng total RNA was used per [TaqMan] TAQMAN® reaction. Tissues tested include the human tissues and several cell lines shown in Tables 3-6. --

In the claims:

Claim 58 has been amended as follows:

58. The method of claim 19 wherein binding of the polypeptide to the test compound is indicated by cleavage of the test compound [the determining comprises an assay for 14094-mediated proteolysis].